REMARKS

The undersigned wishes to express Applicants' appreciation to the Examiner for the courtesy of the telephone conference discussing this matter on July 30, 2003.

The outstanding Office Communication of July 8, 2003 indicated that Applicants' reply filed on June 16, 2003 was not fully responsive to the prior Office Action. The claim amendments were considered by the Examiner to direct the claims to a different invention then that originally presented and elected in the restriction requirement. In this reply and amendment, Applicants have again amended the claims in an earnest attempt to respond to the rejections stated in the Office Action dated January 13, 2003.

The claims pending after this amendment are claims 1, 4-7, 9, 10, 12-15, and 21. Claims 2, 3, 8, 11, and 16-20 stand canceled, without prejudice to refiling in a continuation application. Claim 1 is amended by incorporating the subject matter of claims 2 and claim 8, wherein the compound is a synthetic antisense oligonucleotide compound with at least one modified nucleobase, and which inhibits by at least 10%. These amendments are supported by the original claims 2 and 8, and in the original specification at page 23, lines 8-22 and pages 86-87. Claim 15 has been amended to insert the words "*in vitro*". New claim 21 is a dependent claim stating that the oligonucleotide of claim 1 is at least 30 nucleobases in length and finds support in specification page 12, lines 30-36.

No new matter is introduced by the amended and new claims. Applicants further affirm the correctness of the inventive entity in view of the cancellation of claims.

Rejections Under 35 USC §112, first paragraph

> Claims 15-20 are rejected because the examiner considers that the specification is enabled for methods of inhibiting the expression of human stearoyl-CoA desaturase (SCD) in cells or tissues *in vitro* using antisense, but does not provide enablement for *in vivo* methods.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Cancellation of claims 16-20 moots this rejection as to them. Applicants make no comment on the validity of the rejection vis-à-vis claims 16-20. Applicants have canceled these claims simply to advance prosecution of the remaining claims. Claim 15 has been amended to insert the words "*in vitro*". In view of these amendments, this rejection is satisfied and may be properly withdrawn.

Rejections Under 35 USC §102

> Claims 1, 2, 11, 12 and 14 are rejected:
>
> a. under §102(b) as being anticipated by International Patent Publication No. WO 00/09754 (Stenn).
>
> b. under §102(e) as being anticipated by US Patent Application Publication No. 2002/0151018 (Prouty).
>
> The examiner states that Stenn's 22-mer oligonucleotide primer is fully complementary to SEQ ID NO: 3 and meets all of the structural requirements of the claims. The examiner states that Prouty discloses 21- and 22-mer oligonucleotide primers fully complementary to SEQ ID NO: 3 and meet all of the structural requirements of the claims.

Applicants respectfully request reconsideration and withdrawal of these rejections in view of the above amendments to the claims and the following remarks.

Cancellation of claims 2 and 11 moots these rejections as to them.

Stenn refers to a ***22-mer*** oligonucleotide primer disclosed on page 46, line 13 that is completely complementary to a portion of SEQ ID NO: 3. Prouty refers to 21- and 22-mer sense and antisense primer sequences that are complementary to various regions of SEQ ID NO: 3, which are used to assemble a plasmid construct by polymerase chain reaction. See the first two paragraphs of page 5, col. 1, Examples 2 and 3.

Applicants' claim 1, as amended, incorporates the subject matter of claim 8, which was not rejected under either ground of rejection. None of the primers disclosed by these references falls within the scope of amended claim 1, which provides for a synthetic antisense oligonucleotide having at least one modified nucleobase. Therefore, claim 1 and its dependent claims do not claim the same invention as described by Stenn or Prouty.

In view of these comments and the claim amendments noted above, these grounds for rejection may be properly withdrawn.

Rejections Under 35 USC §103(a)

Claims 1-2 and 4-15 are rejected under 35 USC §103(a) as being unpatentable over the following combination of documents:

(1) International Patent Publication No. WO 00/09754 (Stenn)

(2) Milner et al, **1997** *Nat. Biotech., 15*:537-541 (Milner)

(3) US Patent No. 5,801,154 ("Baracchini").

The examiner states that one skilled in the art would have been motivated to modify the vector expressing an antisense oligo targeted to a nucleic

> acid encoding human SCD, as taught by Stenn, about 8-50 nb as taught by Baracchini, modify the antisense compositions, and formulate them into compositions as taught by Baracchini. Further since methods of screening for antisense to a known gene was routine as taught by Milner, the person of skill would have been expected to find antisense that inhibits express of the desired enzymes because its sequence was known.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

A. Applicants' Invention

Cancellation of claims 2 and 8 moots this rejection as to them.

As amended above, and as specifically taught in the instant specification at page 23, lines 8-11, Applicants claims 1 and claims dependent thereon recite ***synthetic*** antisense sequences that hybridize to human SCD and inhibit expression thereof.

> "The antisense compounds of the invention are synthesized *in vitro* and **do not include** antisense compositions of biological origin, or **genetic vector constructs** designed to direct the *in vivo* synthesis of antisense molecules." (Emphasis added).

Applicants' amended claims are not generic antisense compounds to human SCD. Applicants' claims are directed to novel synthetic antisense compounds having at least a 10% inhibitory activity, which are neither taught nor suggested by the cited references in combination. Applicants claims do not cover generic antisense sequences, which could include sequences capable of hybridizing to human SCD, but which display ***no inhibitory*** activity in Table 1 (see, e.g., SEQ ID NOS: 21, 34-36, 38, 40 and 41,

B. The amended claims are not made obvious by the combination of Stenn, Baracchini and Milner.

Stenn refers to a primer sequence that, when compared with Applicants' target SEQ ID NO: 3, has a nucleotide structure that is 100% complementary to a portion of SEQ ID NO: 3. Stenn refers to its nucleotide sequences as functioning as a probe to detect and/or quantitate human SCD-encoding nucleic acid molecules in a sample (see page 24, lines 11-14), and thus refers to use in a diagnostic assay (page 25, lines 1-19). Stenn also describes methods for screening an "agent" for increasing/decreasing expression levels of SCD (see page 27, lines 1-28), but provides for no description of that "agent" other than an antibody.

Stenn's only reference to antisense technology is limited to references to an ***expression vector*** suitable for use in gene therapy that can encode an anti-sense molecule, which is complementary to and specifically hybridizes with at least a portion of human SCD mRNA to inactivate genes (See, page 31, lines 10-28). Stenn discloses the ***expression vector*** and a pharmaceutically acceptable carrier (See the sentence spanning pages 31-32). Such expression vectors are genetic vectors designed to direct expression of the antisense sequence *in vivo*.

Nowhere does Stenn even refer to or suggest synthetic antisense compounds made *in vitro*, or that such sequences may have a modified nucleobase. Stenn does not describe its 22-mer sequence cited by the examiner as anything other than a primer to amplify the SCD sequence (see pages 45-46). Stenn provides no suggestion that its primer sequence could be designed and used as an individual agent or compound to affect the enzymatic activity of the desaturase enzyme. Stenn suggests

nothing at all about the use of antisense compounds, other than for gene therapy by insertion into ***an expression vector***. Stenn teaches nothing about ***synthetic*** antisense nucleotide ***compounds*** such as claimed by the amended claims.

In summary, Stenn does not disclose or suggest synthetic antisense oligonucleotides. Stenn does not disclose or suggest that such synthetic oligonucleotides have at least one modified nucleoside; or disclose or suggest that when hybridized to the target SCD sequence, such compounds inhibit expression thereof **by at least 10%**.

The remaining two cited secondary documents teach nothing regarding human SCD or antisense sequences capable of inhibiting ***that enzyme's*** activity. Thus, these secondary references do *not*, when added to Stenn, suggest Applicants' claimed invention.

Baracchini refers to synthetic antisense compounds that modulute another *completely unrelated protein* to human SCD, namely multidrug resistance-associated protein (MRP). Baracchini does ***not*** refer to antisense sequences expressed *in vivo* in a genetic construct similar to that of Stenn.

Milner is a review article that refers to synthetic antisense compounds in general and to assays for selecting antisense reagents in general. Milner does ***not*** refer to antisense sequences expressed *in vivo* in a genetic construct similar to that of Stenn.
Milner does not suggest any antisense sequence to human SCD, nor any antisense sequence that inhibits SCD expression by at least 10% of Applicants' claimed invention.

These secondary references do not even mention the protein human SCD. They do not teach or suggest anything about the use of expression vectors for expression of antisense sequences *in vivo*. These references, coupled with Stenn's teachings of a primer and of expression vectors for gene therapy use, do not teach or suggest the synthetic antisense sequences to human SCD that inhibit SCD expression by at least 10%.

This combination of references provides at most the basis for a rejection that it would be "obvious to try" to make synthetic antisense compounds to target SCD and inhibit expression of that enzyme by 10%, simply because others have made synthetic antisense compounds to other ***unrelated*** proteins and because Stenn has suggested ***expression vectors*** carrying antisense sequences to SCD for *in vivo* gene therapy use. The US patent law has long held that the "obvious to try" standard is not the appropriate standard for a determination of patentability.

Thus, the cited references, taken together as a whole, do not make obvious the presently claimed invention.

It is only Applicants who have shown synthetic antisense sequences that hybridize with sequences within human SCD *and* display inhibitory activity of at least 10%. The combined disclosures of Stenn, Baracchini and Milner do not suggest the claimed invention.

In view of the above amendments and these remarks, Applicants' respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,

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